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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,870	09/05/2003	George D. Purvis III	016939.0103 (03-52279-FAI	7307

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
02/26/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/655,870	PURVIS, GEORGE D.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2008*.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9-11,19-21 and 29-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9, 10, 11, 19, 20, 21, 29, 30, and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1, 9, 10, 11, 19, 20, 21, 29, 30, and 31 are pending.

Claims 1, 9, 10, 11, 19, 20, 21, 29, 30, and 31 are rejected.

Claim Rejections - 35 USC § 101

2. The rejection of claims 1, 2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter because the claimed subject matter does not require a tangible result in the Office action mailed 02 July 2008 is withdrawn in view of the amendment to the claims filed 31 December 2008.

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 21, 29, and 30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 21, 29, and 30 are drawn to a computer program on computer readable media. A review of the specification does not show a definition of computer readable media such that excludes an embodiment that is information in a signal. Although the claimed subject matter states that the computer readable media is tangible, the specification does not define computer readable tangible media (and did not contain the phrase at the time of filing). As such an embodiment of the claims read on non-statutory subject matter (In re Nuijten 84 USPQ2d 1495 (2007)). The applicants may overcome the rejection by amendment of the claims to be limited to physical forms of computer readable media described in the specification, or if no description

exists for physical computer readable media, by presenting a statement that the claims do not read on embodiments that are not physical computer readable media that are conventional in the art.

5. Claims 11, 19, and 20 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 11, 19, and 20 are drawn to a process. A process is statutory subject matter under 35 U.S.C. 101 if: (1) it is tied to a particular machine or apparatus or (2) it transforms an article to a different state or thing (In re Bilski, 88 USPQ2d 1385 Fed. Cir. 2008).

The claimed subject matter is not limited to a particular apparatus or machine. The claimed subject matter requires calculation of repulsion terms, potential of mean force terms, and other calculation steps of comparison of protein structure data. None of the steps are limited to require use of a computer, and all steps could be performed mentally or manually. To qualify as a statutory process, the claims should require use of a machine within the steps of the claimed subject matter or require transformation of an article to a different state or thing. Insignificant extra-solution activity in the claimed subject matter will not be considered sufficient to convert a process that otherwise recites only mental steps into statutory subject matter (In re Grams 12 USPQ2d 1824 Fed. Cir. 1989). Preamble limitations that require the claimed process to comprise machine implemented steps will not be considered sufficient to convert a process that otherwise recites only mental steps into statutory subject matter. The applicants are cautioned against introduction of new matter in an amendment.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 21, 22, 25, 27, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite the limitation "computer readable tangible media." The specification at the time of filing did not describe any form of computer readable media.

8. Applicant's arguments filed 31 January 2008 have been fully considered but they are not persuasive. The applicants point to the brief description of figure 1 and also figure 1 itself. However the pointed to locations do not discuss computer readable media and do not provide support for the amendment of 24 April 2008 reciting “computer-readable tangible media.”

Claim Rejections - 35 USC § 102

9. The rejection of claims 1, 11, 21, and 31 under 35 U.S.C. 102(b) as being anticipated by Muegge et al. (Muegge I) in the Office action mailed 02 July 2008 is withdrawn in view of the amendment to the claims filed 31 December 2008.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 9, 11, 19, 21, 29, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muegge et al. (Muegge I) (J. Med. Chem. Vol. 42, pages 2498-2503 (1999), reference G in the IDS filed 07 April 2004) in view of Mitchell et al. (J. Comput. Chem. Vol. 20, pages 1165-1176 (1999), reference U in the notice of references cited mailed 07 March 2006) in view of Muegge et al. (Muegge II) (Med. Chem. Res. Vol. 9, pages 490-500 (1999), reference F in the IDS filed 07 April 2004).

The claims are drawn to methods and apparatus therefor for computing at least two potential of mean force (PMF) scores of a protein-ligand complex from at least two empirically derived minimum binding-energy distances and well-depth values for each atom-pair analyzed. The method comprises calculation of at least two PMF terms for each atom pair analyzed. At least two sets of empirical data are used to derive the PMF of an atom pair. A PMF score of the protein-ligand complex is calculated from each of the at least two PMF scores of the atom-pair that is analyzed, and a structure of the protein-ligand complex is calculated from each PMF score of the protein-ligand complex. The calculated protein-ligand complex structure is compared to an actual analyzed structure of the protein-ligand complex. The extent of agreement between root mean square values of the protein-ligand complexes is used as a measure of the quality of the PMF score. The PMF score of an atom-pair that best agrees with data of the actual analyzed protein ligand-complex is outputted to a user. In some embodiments the at least two empirically derived minimum binding-energy distances and well-depth values are the product of a manual or automatic process.

Muegge I shows especially on page 2499 a method and apparatus for calculation of a PMF of a protein-ligand complex by determining the PMF of each atom pair of the complex.

Muegge I shows on page 2499 that consideration of the van der Waals interactions at short distances is beneficial for determination of the PMF of an atom pair because without such corrections for the short distance repulsion of van der Waals interactions the PMF value would be infinity at short distances. Muegge I shows that if the van der Waals term is larger than 4 kcal/mol, the PMF is overwritten by the van der Waals term value.

Muegge I does not show explicitly sets of empirical data used to derive the PMF of an atom pair or use of empirical data that best agrees with data of an actual analyzed structure of a protein-ligand complex. Muegge I does not show use of the extent of agreement between root mean square values of the protein-ligand complexes as a measure of the quality of the PMF score.

Mitchell et al. shows in the abstract and throughout a method and apparatus for calculation of a PMF score of a protein ligand complex by determining the PMF of each atom pair of the complex. Mitchell et al. shows use of data from the Brookhaven Protein Databank on page 1167, and throughout to aid in determining PMF of atom pairs of interest.

Muegge II shows in the abstract and throughout a method and apparatus for calculation of a PMF score of a protein ligand complex by determining the PMF of each atom pair of the complex. Muegge II shows comparison of root mean square deviations of multiple ligands on pages 492- 497.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the empirical data of Mitchell et al. to aid in determining the PMF values of Muegge I because Mitchell et al. shows use of empirical data in determining PMF values. It would have been further obvious to use empirical data that best agreed with the protein

ligand under examination to improve accuracy of the method. It would have been further obvious to consider the root mean square deviations of data used in the method of Muegge II to perform the comparisons because Muegge II shows that comparison of root mean square deviations is a useful method to compare structures.

12. Claims 1, 9, 10, 11, 19, 20, 21, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muegge et al. (Muegge I) in view of Mitchell et al. in view of Muegge et al. (Muegge II) as applied to claims 1, 9, 11, 19, 21, 29, and 31 above and further in view of Morris et al. (J. Comput. Chem. Vol. 19, pages 1639-1662 (1998), cited as reference L in the IDS filed 07 April 2004).

The claims are drawn to a method and apparatus of determining a PMF score for a protein ligand complex in which data used to generate a PMF of atom pairs in the complex is determined by a genetic algorithm.

Muegge I in view of Mitchell et al. in view of Muegge II as applied to claims 1, 9, 11, 19, 21, 29, and 31 above does not show data used to generate a PMF of atom pairs in the complex determined by a genetic algorithm.

Morris et al. discloses methods of using genetic algorithms in docking programs to predict bound conformations of flexible ligands. Morris et al discuss the known methods of three dimensional protein-ligand analysis, which include the automated determination of minimized free energy conformations. Morris et al. discusses known genetic algorithms (page 1641), and their use in docking programs. The genetic algorithm is used for searching the global computational space to identify a most fit structure of the protein-ligand interaction. The AUTODOCK program performs a specified number of dockings, then carries out conformational

cluster analysis on the docked conformations to determine which are similar ranked by increasing energy. The "fitness" of the structure can be based on a variety of parameters. AUTODOCK uses a dispersion/repulsion term, a hydrogen bonding term, and a screened Coulombic electrostatic potential. MSMS is used to compute the analytical molecular surfaces, which is analogous to a well-depth value. Morris et al. show that their combination of a genetic algorithm, free energy calculations, and docking/design programs provide faster and more reliable results.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the known computation methods of genetic algorithms to the methods of Muegge I in view of Mitchell et al. in view of Muegge II as applied to claims 1, 9, 11, 19, 21, 29, and 31 above for scoring PMF functions of protein-ligand interactions because Morris et al. shows that genetic algorithms provide faster and more successful searching of free energy conformations.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John S. Brusca/
Primary Examiner, Art Unit 1631

jsb